SUPPORT AND MANAGEMENT FOR THE PROJECT:
"EFFECTS OF THE CHORNOBYL ACCIDENT ON THYROID CANCER AND LEUKEMIA/LYMPHOMA"
CONTRACT BETWEEN NATIONAL CANCER INSTITUTE AND THE TRUSTEES OF
COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK
QUARTERLY PROGRESS REPORTS, JANUARY 1, 2000 - MARCH 31, 2000

I. INTRODUCTION

This report covers activities carried out during the second quarter of the third year of the contract between the National Cancer Institute (NCI) and Columbia University for the support of thyroid cancer in children in Belarus and Ukraine and leukemia in clean-up workers in Ukraine.

With regard to the thyroid studies, the focus has been on monitoring recruitment of study subjects and the implementation of new data management systems, ultrasound image archiving in Belarus, proceeding with supply and equipment purchasing in both studies and preparing for an equipment inventory in Belarus, Ukraine..

With regard to the study of leukemia in the clean-up workers in Ukraine, emphasis has been placed on the completion of a protocol for the Phase II study.

A training workshop on cohort analysis using the the EPICURE statistical program was organized by the Columbia investigators. The workshop was held in February 2000 in Kiev and was attended by individuals concerned with analysis from all three studies.

II. SUMMARY OF MAJOR ACTIVITIES

1. Thyroid Studies:

A. Individual Trips by Columbia Team Members and Consultants: A number of Columbia team members and consultants made trips to Belarus and Ukraine during the quarter and detailed reports for these trips have been forwarded to NCI. Copies of these trip reports are available upon request. The following trips were made:

Dr. Howe: January 27-28, Kiev, Ukraine (co-chaired meeting of dosimetry groups from Belarus and Ukraine); March 20-21, 2000, Kiev, Ukraine (reviewed the data management system and study recruitment progress).

Dr. Mitchell: January 29-February 9, 2000, Minsk, Belarus (reviewed the ultrasound clinical and image handling systems and staffing of the DCC, database design, data entry and editing); February 10-12, 2000, Kiev, Ukraine (reviewed progress of data entry, data edits and study status reports).

Dr. Heitjan: February 7, 2000, Minsk, Belarus (had to cut trip short for personal reasons; reviewed the progress of the DCC).

Dr. Brill: January 31-February 5, 2000, Minsk and Gomel, Belarus (reviewed ultrasound imaging and profiling).

Ms. Sally Hodgson: March 16-17, 2000, Minsk, Belarus; March 20-23, 2000, Kiev, Ukraine (prepared for equipment inventory in both studies).

Dr. Fink: March 17-18, 2000, Minsk, Belarus; March 20-21, 2000, Kiev, Ukraine (reviewed laboratory testing in both studies).

Please see Appendix A for a brief summary of these trips.

B. Establishment of a New Data Management System in Ukraine: Negotiations have continued with Dr. Daniel Hryhorczuk at the University of Illinois in Chicago to form a service agreement with Columbia University for May to September 2000. This agreement is being sought in order that the University of Illinois, through a unit already established in the Institute of Pediatrics in Kiev, can provide data management support and help erase the serious backlog in data entry. A meeting was held in Kiev on March 21, 2000 with Drs. Howe and Hryhorczuk and Ms. Hodgson where

arrangements were made for Ms. Hodgson together with Dr. Leslie Nickels of the University of Illinois (Chicago) to proceed to the finalization of this agreement.

2. Leukemia Study

A. Individual Trips by Columbia Team Members and Consultants: A number of Columbia team members and consultants made trips to Ukraine during the quarter and detailed reports for these trips have been forwarded to NCI. Copies of these trip reports are available upon request. The following trips were made:

Dr. Howe: January 24-26, 2000, Kiev, Ukraine (discussed proposal draft with Ukrainian investigators); February 9-11, 2000, Kiev, Ukraine (discussion of further revisions to proposal and budget); March 20-21, 2000, Kiev, Ukraine (finalization of proposal and further budget discussions).

Dr. Finch: January 25-27, 2000, Kiev, Ukraine (discussion of hematological issues in proposal for a Phase II study).

Please see Appendix A for a brief summary of the trip reports.

B. International Dosimetry Group: Dr. Howe attended a meeting of this group in Lyon, France on March 23-24, 2000, with regard to assessing dosimetric methods and reviewing dosimetric estimates.

C. Proposal for a Case Control Study of Leukemia Among Chornobyl Cleanup Workers in Ukraine: Dr. Howe took the lead from the US side in preparing a proposal for a possible Phase II study of leukemia in clean up workers in Ukraine. As above, in this regard Dr. Howe traveled to Ukraine in order to have direct contact between himself and the Ukrainian investigators to discuss issues involved in the planning and writing up of a proposal for a possible Phase II study, and to

discuss issues involved in the implementation of the study should it be funded. He also worked closely with Professor J. David Burch and Dr. S. Finch, who is both an investigator in the proposed Phase II study and a consultant to Columbia University on the final version of the proposal document which was expected to be forwarded to NCI early in April, 2000.

3. Training Workshop on Cohort Analysis Using EPICURE Computer Program:

A training workshop on cohort analysis using the EPICURE computer program was held in Kiev, Ukraine from February 14 to 18, 2000 with the attendance of 21 relevant individuals from both thyroid studies and the leukemia study in Belarus and Ukraine. The course was also attended by Dr. G. Howe and Dr. L. Zablotska from Columbia University and was taught by Dr. Michael Vaeth, Chairman of the Department of Biostatistics, University of Aarhus, Denmark. Dr. Vaeth is an expert on analyzing radiation data using EPICURE.

Dr. Vaeth presented examples of analysis of radiation data using AMFIT and PECAN models from the EPICURE computer program. Approximately half of the participants from Belarus and Ukraine work in dosimetry and data coordination while the rest are epidemiologists and statisticians. Drs. Howe and Zablotska presented possible future uses of the EPICURE program in all three studies.

The format of the workshop involved a daily two hour lecture followed by "hands on" sessions during which the students were given the opportunity to analyze real data provided by Dr. Vaeth on computer work stations. These sessions were followed daily by a question and answer period.

III. UNIVERSITY OF UTAH SUBCONTRACT

Intercomparison:

Measurements of enamel samples for the joint UU-SCRM intercomparison have been completed but results have not yet been fully analyzed.

Response to the report

Study of Leukemia, Lymphoma and other hematologic diseases among cleanup workers in Ukraine, following the Chernobly accident:

Report on Phase I of the study: 1997-1999.

Comments on the potential of EPR to validate doses in the range of 10 to 100 mGy.

According to the report, the vast majority of doses to liquidators are in the range of 10 to 100 mGy. Since the success of the epidemiological study revolves around the accurate assessment of doses in this range, two questions arise, 1) can a non-physical method (ODR, etc) accurately estimate doses in this range and 2) can EPR be used to assess the reliability of those other methods in the dose range of interest. The later is important since it is unlikely that sufficient numbers of healthy teeth can be collected to provide more than cross checks on the accuracy of the other methods.

A number of studies have addressed both the precision (Schabl 1996, Haskell et al. 1997C, Hayes et al. 1997) and accuracy (Toyoda et al. 1994, Schauer et al. 1994, Polyakov et al. 1995, Grün 1996) with which EPR techniques can retrospectively reconstruct radiation doses to tooth enamel. Similarly, related efforts have focused on attaining both a combined high accuracy and high precision dose reconstruction (Galtsev et al. 1996, Chumak et al. 1996, Haskell et al. 1997A, Haskell et al. 1999B). In a recent paper, Haskell et al. (1997B) delineate many major error introducing effects in EPR dosimetry of tooth enamel. A follow up study by Haskell et al. (1999B) demonstrated that when all the error introducing effects previously delineated in Haskell et al (1997B) are corrected for, measurement precision can be decreased below 5 mGy (1 standard deviation) at the 100 mGy dose level.

Additional information is available from the most recent International EPR Intercomparison (Wieser et al., 2000). Eighteen EPR laboratories measured gamma-ray doses to whole teeth in the range of 100 to 1000 mGy. Of those laboratories 6 produced results with correlation coefficients > 0.99, the

mean reported dose for those laboratories was 96 ±88 mGy (1σ). Figure 1. shows results from the University of Utah. Some concern was raised about the accuracy of source calibration of the laboratories, however the calibration error introduced into measurements of doses at the 100 mGy level would likely be less than 15%. With accurate source calibration the uncertainty at the 100 mGy level would be approximately ±75 mGy based on results of the intercomparison.

Results of the 2nd International EPR Intercomparison (Wieser et al., 2000). appear to conflict with the results of Haskell et al (1997B). The 6 laboratories in the 2nd Intercomparison mentioned in the previous paragraph reported measurement uncertainties at the 100 mGy level of 45± 43 mGy. According to Haskell et al (1997B), the measurement uncertainty at the 100 mGy level could be reduced to less than 10 mGy. The apparent contradiction results from 1) measurement uncertainties, 2) biological factors and 3) environmental factors which were minimized or eliminated in the precision study but are uncontrolled in the intercomparison study. The difference lies in 1) optimization of measurement parameters and procedures, and 2) prior measurement of a baseline EPR signal (the native signal plus any previous X-ray dose as well as any UV component) in the precision study. The later is not possible for absolute retrospective measurements but is useful where multiple sections from the same tooth are measured for determination of dose versus depth profiles due to diagnostic X-ray exposure (Hayes et al., 2000).

Biological uncertainties: The so called "native" signal of enamel is currently a primary source of uncertainty in EPR measurements of teeth. This signal has an amplitude equivalent to several hundred mGy and it overlays the EPR signal used for dosimetric analysis. Numerous methods have been developed for dealing with the native signal, however, none has proven entirely satisfactory. Dental caries is another source of potential error in EPR measurement of teeth although published reports concerning its effects on dose measurement are contradictory (Brik et al., 1996, Romanyukha et al., 1999 Sholom et al., 1999).

Environmental uncertaintes: These include contribution from dental and medical x-rays as well as contribution to the dosimetric signal from solar UV exposure. The former can be addressed to some extent using differential analysis of inner and outer halves of teeth and the latter by limiting analysis to molars and premolars.

Exposure uncertainties: The dose received by tooth enamel may not be well correlated with dose received by film badges or even bone marrow. Aside from well known energy dependencies, uncertainties associated with positional, physical and biological variations (body fat, muscle, etc.) which effect correlation of enamel dose, film badge dose and bone marrow dose have not been well studied and could themselves be large.

Removing Native single uncertainties. If it is assumed that the native signal of a given, healthy tooth is uniform throughout its enamel, then measurements of enamel sections of the same tooth can be made with the native signal treated similarly for each section. Any error associated with the native signal will be of the same sign and magnitude for each section and the relative uncertainties between sections will be independent of the native signal. The accuracy of the dose differential between sections will be independent of uncertainties associated with the normal tooth to tooth variations of the native signal. Thus the accuracy of determination of dose vs depth profiles in a single tooth can far exceed that of measurements of dose to teeth from different individuals. Since uncertainties associated with tooth to tooth variations of the native signal can be large, efforts at accurately modeling the native signal, reducing its size, or even assessing the extent of variation in the native signal of different teeth would be helpful. Several attempts have been made at reducing the size of the native signal in enamel, however caution should be exercised in adopting such methodologies since seemingly successful removal of the native signal in dentin resulted in large changes in the dentin's radiation sensitivity (Kenner et al.).

In light of these uncertainties it is unlikely that improvements in precision due to instrumentation upgrades will significantly improve dose uncertainties in the range of 10 to 100 mGy.

Recommendations

Non-destructive testing of low dose samples.

Sensitivity variations will likely result in increases of uncertainties by less than 10-15%, compared to the 100+% uncertainties that can be introduced from other variables. It is, therefore, highly advisable to perform non-destructive measurements on low dose teeth. This will result in 1) reduction in measurement time (no need for additional irradiations and annealings) as well as 2) retention of valuable samples (future improvements in preparation techniques could conceivably be applied to non-destructively measured teeth, but not to those given additive doses)

Examination of methods for reducing effects of the Native EPR signal.

The importance of the native signal is evidenced by the many methods currently available for minimizing its influence. Methods include selective saturation (Ignatiev et al. 1995), spectral simulation (Wieser et al. 2000), spectral deconvolution (Jonas 1995), amplitude adjusted native signal subtraction (Haskell et al., 1999B) and whole spectrum modified native signal subtraction (Skvortzov et al. 1995). All have been demonstrated to be viable methods for EPR dosimetry of tooth enamel but none has reduced the overall uncertainties of dose estimation below the 30 mGy level. Reduction of native signal interference would result in dramatic improvements in accuracy of EPR dosimetry of enamel.

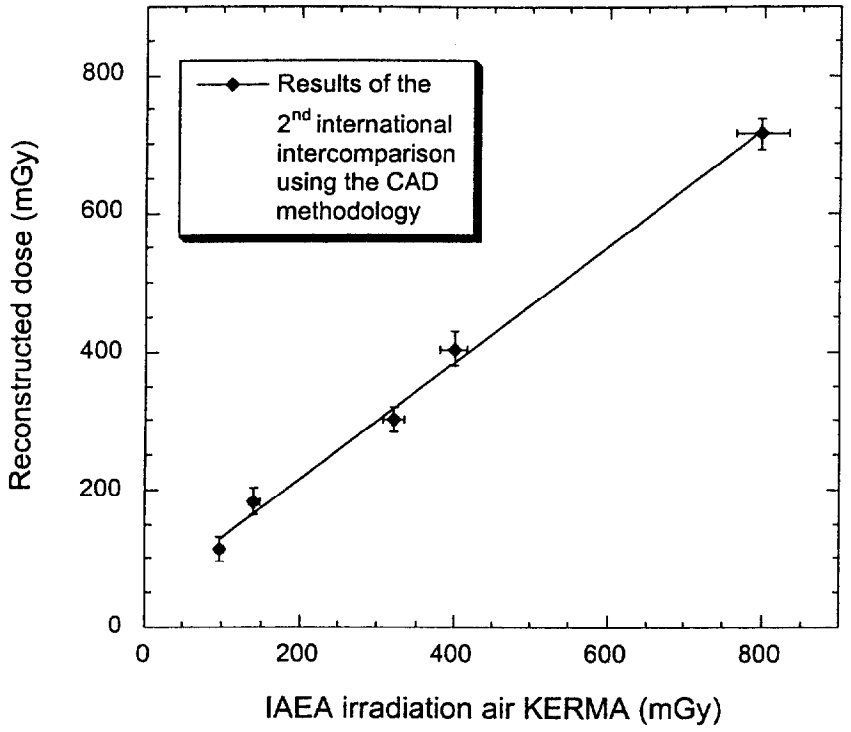

Figure 1. Results of dose estimates performed by Center for Applied Dosimetry as part of the 2nd International EPR Intercomparison.

References:

Brik, A., Radchuk, V., Scherbina, O., Matyash, M. and Gaver, O. (1996). Metomorphic Modifications and EPR Dosimetry in Tooth Enamel, Appl. Radiat. Isot., 47, 1317-1319.

Chumak V., Bailiff I., Baran N., Bougai A., Dubovsky S., Feedosov I., Finin V., Haskell E., Hayes R., Ivannikov A., Kenner G., Kirillov V., Khlamidova L., Kolesnik S., Liidja G., Likhtarev I., Lippmaa E., Maksimenko V., Meijer A., Minenko V., Pasalskaya L., Past J., Puskar J., Radchuk V., Sholom S., Skvortzov V., Stepanenko V., Vaher U. and Wieser A. (1996) The first international intercomparison of EPR dosimetry with teeth: first results. *Appl. Radiat. Isot.* 47, 1281-1286.

Galtsev V. E., Galtseva E. V. and Lebedev Ya. S. (1996) Optimal registration conditions for tooth EPR dosimetry at low accumulated dose. *Appl. Radiat. Isot.* 47, 1311-1316.

Grün R (1996) Errors in dose assessment introduced by the use of the "linear part" of a saturating dose response curve. *Radiat. Meas.* **26**, 297-302.

Haskell, E. H., Kenner, G. H., Hayes, R. H., Sholom, S. V. and Chumak, V. V. (1997A) An EPR Intercomparison using Teeth Irradiated Prior to Crushing. *Radiat. Meas.* **27**, 419-424

Haskell E. H., Hayes R. B., Kenner G. H., Sholom, S. and Chumak V. (1997B) EPR techniques and space biodosimetry. *Radiat. Res.* **148**, S51-S59.

Haskell E. H., Hayes R. B. and Kenner G. H. (1997C) Improved accuracy of EPR dosimetry using a constant rotation goniometer. *Radiat. Meas.* **27**, 325-329.

Hayes R. H., Haskell E. H., Kenner G. H. (1997) A mathematical approach to optimal selection of dose values in the additive method of EPR dosimetry. *Radiat. Meas.* 27, 315-323.

Hayes R B, Haskell E H, Kenner G H and Barrus J K. (2000) A virtually non-destructive EPR technique accounting for diagnostic X-rays. Presented at the 9th International Conference on Luminescence and Electron Spin Resonance Dating, Rome, 6-10 September 1999..

Jonas, M. (1995) Spectral Deconvolution of the ESR Dating Signal in Fossil Tooth Enamel. *Quat. Sci. Rev.* **14**, 431-438.

Polyakov V., Haskell E., Kenner G., Huett G. and Hayes R. (1995) Effect of mechanically induced background signal on EPR dosimetry of tooth enamel. *Radiat. Meas.* 24, 249-254.

Toyoda S., Sumitomo H., Ikeya M. and Ishii H. (1994) Separation of CO_2^- signal from a spectrum of irradiated tooth enamel in ESR dosimetry. *Assessment of the Health and Environmental Impact from Radiation Doses Due to Released Radionuclides*, Proceeding of the International Workshop at Chiba, Japan, Jan. 18-20.

Schauer A., Desrosiers M. F., Le F. G., Seltzer S. M. and Links J. M. (1994) EPR dosimetry of cortical bone and tooth enamel irradiated with X and gamma rays: study of energy dependence. *Radiat. Res.* **138**, 1-8.

Schabl G., EPR-Spectrometry on calcified tissues: methodological considerations concerning reliable dose reconstruction at low doses. Proceedings International Workshop on Radiation Exposures by Nuclear Facilities, July 9-12, 1996, Portsmouth, U.K.

Sholom, S.V., Haskell E.H.; Hayes R.B.; Chumak V.V.; Kenner G.H.; (1999). EPR-dosimetry with carious teeth. Presented at the 9th International Conference on Luminescence and Electron Spin Resonance Dating, Rome, 6-10 September 1999..

Skvortzov V. G., Ivannikov A. I. and Eichhoff U. (1995) Assessment of individual accumulated irradiation doses using EPR spectroscopy of tooth enamel. *J. Mol. Struct.* **347**, 321-330.

Romanyukha, A.A., Hayes, R.B., Haskell, E.H., and Kenner, G.H. (1999) Geographic variations in the EPR spectrum of tooth enamel. Rad. Prot. Dosim. 84, 445-449.

Wieser A, Onori S, Fattibene P, Aragno D, Romanyukha A, Ignatiev E, Koshta A, Skvortzov V, Ivannikov A, Stepanenko V, Chumak V, Sholom S, Haskell E H, Hayes R B and Kenner G. H. (1999) Comparison of sample preparation and signal evaluation methods for EPR analysis of tooth enamel. Appl. Radiat. Isot. (at press).

Wieser,A., K. Mehta, S. Amira, D. Aragno, S. Bercea, A. Brik, A. Bugai, F. Callens, V. Chumak, B. Ciesielski, R. Debuyst, S. Dubovsky, O.G. Duliu, P. Fattibene, E.H. Haskell, R.B. Hayes, E.A. Ignatiev, A. Ivannikov, V. Kirillov, E. Kleschenko, N. Nakamura, M. Nather, J. Nowak, S. Onori, B. Pass, S. Pivovarov, A. Romanyukha, O. Scherbina· A.I. Shames, S. Sholom, V. Skvortsov, V. Stepanenko, D.D. Tikounov, S. Toyoda. (2000) The 2nd International Intercomparison on EPR Tooth Dosimetry. Presented at the 9th International Conference on Luminescence and Electron Spin Resonance Dating, Rome, 6-10 September 1999

IV. OUTLINE OF ADMINISTRATIVE ACTIVITIES

Administratively, the second quarter of Year 3 concentrated on preparation of financial estimates of anticipated expenditures to year end, purchasing, travel and translation.

Expenditure estimates were first based on the figures sent to Columbia by NCI that originated in Belarus and Ukraine and were sent to NCI on form 2706. The approved purchase lists were then sent out for bids, bids were evaluated and final vendors selected. Utilizing the pricing obtained from bids, S. Hodgson revised the cost estimates for study purchases, circulated the cost estimates through Columbia and sent the revised list to NCI. Concurrently, D. Illian worked to initiate purchase orders. The purchase orders are now being completed and some of the supplies have begun to arrive in Belarus and Ukraine.

Questions from NCI regarding estimated expenditures by year end were received and reviewed. S. Hodgson worked with D. Illian and S. Kokoreva to review financial records in order to prepare responses.

Additionally, the second quarter included the EPICURE Workshop in Kiev that S. Kokoreva and D. Illian worked to support. Arrangements were made for travel and materials required were produced. At the same time S. Hodgson learned that L. Zablotska's H-1 Visa was approved and responded by undertaking the actions necessary to hire her as a Staff Associate at Columbia. The hiring of L. Zablotska as a Staff Associate, the originally budgeted position, was not possible without the change in her Visa to H-1.

The quarter ended with an administrative management trip to Minsk and Kiev where S. Hodgson worked with I. Masnyk and D. Fink to try to find solutions for some of the ongoing problems of purchasing and delivery of supplies and equipment. S. Hodgson has been working with D. Illian to implement some of the ideas garnered on that trip.

V. FUTURE ACTIVITIES

Future activities will continue to center on "on the ground" involvement of the Columbia team and consultants in the two thyroid studies and the leukemia study, should the latter be funded. Frequent visits by members of the Columbia team and consultants to Belarus and Ukraine are necessary to monitor on going study progress and the establishment of second screening procedures in the two thyroid studies.

With regard to the thyroid study in Ukraine, emphasis will be placed in the next quarter on the possibility of the establishment of a subcontract with the University of Illinois to provide continuing data management. With regard to the thyroid study in Belarus attention will be focused on improving recruitment rates, monitoring the progress of the preparation of a code book, data quality reports and

a data management operations manual. The Columbia team also expects to be involved in the establishment of the Gomel center.

A review of cytology and pathology cases is planned for both Belarus and Ukraine in order to provide ongoing quality assurance of cytopathologic diagnoses. This will be accomplished by reviewing a sample of fine needle aspiration biopsies in conjunction with cytology forms.

Continued emphasis will also be placed on both thyroid studies to establish uniform clinical criteria so that the data from both countries are comparable and can be integrated into a single data base.

In terms of laboratory testing a plan will be developed to define reference ranges for laboratory results in both Belarus and Ukraine. This is necessary since, at the moment, there is no clear cut definition.

In terms of supplies and vacutainers in both thyroid studies it is anticipated that a re-calculation of requirements of these items will be done.

With regard to the proposed Phase II study of leukemia in liquidators in Ukraine, a series of necesssary tasks in the interim period before full funding would start have been developed; the Columbia team will be heavily involved in ensuring that these tasks are completed before the start of the Phase II study.

APPENDIX A

SUMMARY OF INDIVIDUAL TRIP REPORTS

1. Dr. Finch, January 25-27, 2000, Kiev, Ukraine

The principal hematology objectives for the meeting in Kiev at the Research Center for Radiation Medicine were to firm up plans for the conduct of the implementation phase of the study of leukemia, myelodysplasia and multiple myeloma in liquidators. Joint meetings were held with key epidemiologists at the Center in order to coordinate plans for case ascertainment and verification. Leukemia related diagnoses to be investigated were identified and tentative plans were made for the equipment, supplies and travel required for completion of the study.

2. Dr. Mitchell, January 29-February 9, 2000, Minsk, Belarus; February 10-12, 2000, Kiev, Ukraine

Minsk: Ultrasound Imaging - Drs. Mitchell and Brill met with the staff of the DCC, the Dispensary and Dr. Drodz from Aksokovchina concerning the ultrasound clinical and image handling systems. We met with Drs. Rzeytsky, Drodz, Shaverda (ultrasonographer), with Boris, and Arthur. Drs. Brill and Mitchell met with both Nadya Leskova, Arthur Kushinnikov regarding the image quality control, archiving, software and hardware needs.

Data Coordinating Center Meetings: Drs. Heitjan, Thomas and Mitchell met with Nadya Leskova to discuss staffing of the DCC, database design and structure, data entry and editing. Separately, Dr. Mitchell met with Nadya and Arthur to discuss equipment and supply needs. Dr. Mitchell brought along form labels to assist with immediate supply needs. Dr. Mitchell and Arthur met with hardware and software suppliers and a detailed report of equipment and supply needs was prepared and faxed back to Sally Hodgson at Columbia.

Kiev: Dr. Mitchell met with Sasha Kostin and Anna to discuss progress with data entry, data edits and study status reports. Drs. Masnyk and Mitchell conducted a site visit of the UIC Data Management Center and discussed with Alexander Zvinchuk the thyroid project data entry and quality control needs. DCC equipment and software needs were discussed with Sasha Kostin.

2. Dr. Brill, January 31-February 5, 2000, Minsk and Gomel, Belarus:

The goal of the trip to Minsk regarding the thyroid study was to accomplish two tasks: (1) determine the nature of the ultrasound and image transmission systems implemented in the Gomel area of the study and (2) for Dr. Mitchell and Dr. Brill to work with the DCC staff setting up the systems for archiving and distribution of ultrasound image data. The distribution system they planned will provide CD ROM access to images from all previously studied patients by time period. Multiple copies will provide data for the different locations where repeat patient studies will be conducted to provide a record of the previous studies for comparison with current images.

The systems in Gomel were reviewed with the staff of the Radiation Medicine Dispensary in Gomel with the assistance of Professor Yamashita. The recording media, and the formats used are compatible with what is being done in Minsk and Kiev and the opportunity for sharing of data appears to be quite promising.

The needs for new computing equipment were specified by Dr. Mitchell thus facilitating an expeditious ordering of such equipment. A similar approach to ordering of other supplies and equipment is needed to overcome the uncertainties and delays that slow down the current ordering process.

3. Dr. Heitjan, February 7, 2000, Minsk, Belarus.

Dr. Heitjan's February trip to Minsk and Kiev regarding the thyroid studies was cut short by the death of his father. However, Dr. Heitjan did spend one day at the DCC in Minsk with Drs. Mitchell and Thomas reviewing the progress of the DCC since his last visit in September of 1999 and

formulating plans for revising the code book and for a new batch data editing and data quality control reporting system. Specific recommendations are included in Dr. Heitjan's trip report.

4. Ms. Sally Hodgson, March 16-17, 2000, Minsk, Belarus; March 20-21, 2000, Kiev, Ukraine
Both Belarus and Ukraine maintain supply and equipment lists that note dates of receipt and disposition of each item. Utilizing their background information in conjunction with Columbia University records and the records provided by NCI, it is feasible to conduct an inventory and initiate a bar code system. Tracking in subsequent years should be fairly easy as it is clear that each project is eager to comply with our requirements. Additionally, I am much more optimistic about decreasing the need for on-ground purchases by Columbia University. As Belarus and Ukraine become more open to the West, it becomes easier to follow standard Columbia purchasing procedures. While Belarus is, by far, the least Westernized country, it is possible to begin to locate at least some vendors to do business utilizing purchase orders and wire transfers to Western accounts.

5. Dr. Fink, March 17-18, 2000, Minsk, Belarus; March 20-21, Kiev, Ukraine
Minsk: A review of the laboratory aspects of the study uncovered four major issues of concern. First, the laboratory staff is not adequately responding to indications of analytical problems. Clear-cut signs of an analytical issue in both the calibration curves and the quality control data for anti-TPO were ignored. The laboratory director and staff will require further education and increased assistance in monitoring quality control results. Second, we continue to have problems getting adequate supplies to Belarus in a timely fashion. Third, we must address the issue of establishing reference ranges for the analytes measured in the study. The ranges reported by the Brahms reagents have not been validated in a Belarussian population and "It is recommended that each laboratory establish its own reference range based on representative patient populations...." Fourth, we will need to adjust the data collection, storage and analysis to take into account the past (and future) changes in methods and normal ranges so that result interpretations from different periods can be combined.

Kiev: The laboratory testing seems to be progressing in a satisfactory fashion except for the problems with providing the project with an adequate supply of reagents. The laboratory staff is adhering to quality control protocols but probably needs additional training and assistance in quality control procedures. As in Belarus, we must address the issue of establishing reference ranges for the analytes measured in the study. The ranges reported by Brahms have not been validated in a Ukrainian population and "It is recommended that each laboratory establish its own reference range based on representative patient populations..." The data collection, storage and analysis must be able to deal with the past (and future) changes in methods and normal ranges so that result interpretations from different periods can be combined.

APPENDIX B

January 1, 2000-March 31, 200

January 24-26, 2000	Phase II Proposal Discussions - Kiev, Ukraine (Dr. Howe)
January 25-27, 2000	Phase II Proposal Discussions - Kiev, Ukraine (Finch)
January 27-28, 2000	Dosimetry group meeting (Drs. Howe, Co-Chair, and Finch)
January 29-February 12, 2000	Review of computer systems- Belarus and Ukraine (Dr. Mitchell)
January 31-February 5, 2000	Ultrasound review - Belarus (Minsk, Gomel) (Dr. Brill)
February 7, 2000	Review DCC - Belarus (Dr. Heitjan, returned home for family emergency)
February 9-11, 2000	Phase II Proposal Discussions - Kiev, Ukraine (Dr. Howe)
February 14-18, 2000	Epicure Workshop (Howe, Zablotska, Vaeth)
March 2, 2000	ACERER Meeting at Columbia (Schletty, Matanoski, Howe, Burch, McConnoll, Fink, Greenebaum, Hodgson, Illian, Zablotska, Kokoreva)
March 16-17, 2000	Clincial and Administrative Reviews in Minsk (D. Fink and Sally Hodgson)
March 20-21, 2000	Clinical & Data Management Review in Kiev (Drs. Howe, Fink)
March 20-23, 2000	Administrative Review in Kiev (Ms. Hodgson)
March 21, 2000	Meeting (Howe, Hryhorczuk, Hodgson)